THE

ETIOLOGY OF TUMORS.

A PAPER READ BEFORE THE

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THE ETIOLOGY OF TUMORS

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THE etiology of tumors is a dark chapter in pathology. I seized with great pleasure the opportunity to read a paper on this topic, as it concerns questions in which many of us are deeply interested. During the last few years I have spent a great deal of time in the study of the cause of tumors, but, as will be seen, with only moderate success. It is to the discussion of this subject by the members of this Society and to criticism which is to follow that I look forward with deep interest for practical points, information and instruction.

Not only is the etiology of tumors insufficiently treated in the respective text-books, but the literature of the subject is not generally accessible, hence I think it will be a welcome addition to American medical literature if I represent each and all of the author's views concisely, but fully enough to avoid misrepresentations. Then follow all the experimental researches concerning the inoculability and origin of tumors, including researches made by myself and other students of pathology in the pathological laboratory of the University of Pennsylvania.

I. VIEWS OF AUTHORS.

We shall first have to consider what new formations authors include under the heading of tumors, in as much as this stands in direct relation to their view of the etiology. Much less discrepancy between the views will be observed if we define this more closely.

In the sense of Virchow, any circumscribed elevation over a given surface or any excessive enlargement, is considered a tumor. The products of specific inflammation such as tubercle, gumma, glanders, lupus and lepra, also the cysts and most of the hypertrophies would consequently belong here. Those authors who regard the products of specific inflammation as tumors, naturally draw from this the inference that most of the tumors are the result of inflammation. Other authors exclude from the category of tumors the above-mentioned inflammatory products, together with cysts and hypertrophies and hence they class with tumors only new formations for which an evident cause had not been proven, explaining the etiology of the latter by all kinds of hypotheses.

Authors change their views occasionally, and some now take a stand in the question of the histogenesis and etiology of tumors different from that expressed in previous writings. I have been careful to represent the doctrines as they stand to-day.

The different authors and their views of the etiology of tumors can conveniently be classed in the following five groups[1].

1. Predisposition and inflammatory theory: Virchow, S. D. Gross, Woodward, Samuel, Wagner, Birch-Hirschfeld, Cornil and Ranvier, Perls, Tyson, S. W. Gross, Fitz.[2]

2. Dyscrasia theory: Rokitansky, Paget, Billroth, Simon.

3. Embryonal theory: Cohnheim, Thiersch, Waldeyer, Lücke, Maas, Hasse, Epstein.

4. Idiopathic or spontaneous theory: Rindfleisch, Stricker, Nancrede, Payne.

5. Nervous theory: Van der Kolk, Lang, Snow.

1. The Predisposition and Inflammatory Theory.

The idea of regarding tumors as inflammatory products is not new. John Burns[3] described medullary cancer as a sponge-

[1] I enumerate here only those authors who, to my knowledge, have expressed themselves more or less definitely on this particular subject.

[2] This grouping of authors concerns only their views on etiology; those on histogenesis would require different grouping.

[3] Dissertation on Inflammation, Glasgow, 1800.

like inflammation. The French school in the early part of this century, particularly Broussais[1] (1826) regarded all tumors as products of chronic inflammation. More than this, even Galen[2] in the second century, 1700 years ago, says that "nasal polyps are due either to inflammation or develop from a node (Phyma) or from germinal matter (Blastema)." Virchow says that many tumors are undoubtedly the products of inflammation and that it is difficult to draw a line separating them from those tumors whose origin cannot be ascribed to inflammation.

In the etiology of tumors there are after Virchow to be considered three causal conditions: first, local causes upon which depend the development of a tumor in a particular place; second, a general predisposition; third, a general cause, which, for the sake of convenience is made to relate to the fluids of the body and is called dyscrasia or cachexia. "Cachexia," Virchow says, "is not always present. It never has been observed in the beginning of the formation of the tumor, but always as subsequent to it, and the condition can be brought about by other than cancerous juices. Cachexia will manifest itself only in such persons in whom the stomach liver or lymphatic apparatus becomes primarily or secondarily affected by cancer or anything else. There is a physiological predisposition in certain tissues to be more readily attacked and sooner affected by disease than others. Highly organized tissues are very little predisposed to excessive abnormal formative activity. The latter occurs more in the connective tissue and its derivatives and the lymphoid and epithelial tissue; in the epithelial tissues, the new formation takes its departure usually only from the younger undeveloped cells (*i. e.* from the lower stratum of the *rete mucosum*). This predisposition in tissues may be acquired, it does not need to be inherited."

"In opposition to the humoro-pathological doctrine, is brought the neuro-pathological by which several enthusiastic neuropathologists sought to explain neoplastic formations. These

[1] Broussais, Histoir des Phlegmasies Chroniques, Paris, 1826.

[2] De tumoribus praeter naturam. Cap. 17, quoted after Virchow, Die Kr. Geschwülste, I., p. 35.

authorities cite such causes as care, distress, lesions of nerves and serious febrile disturbances. These causes are mostly brought forward in case of cancer of the stomach; but the arguments are very weak. Statistics show that cancer, and especially cancer of the stomach, occurs more often in the higher, wealthier classes than among the poor. The nervous symptoms are caused by the presence of the cancer. In cases of all tumors the nerves may, on account of weakness and disturbance of nutrition, be a predisposing cause and no more." * * * * *

"Not being able to find the cause of tumors in the blood or nervous system we naturally turn to the tissues themselves from which tumors proceed. An important fact to be mentioned in this connection is a local disposition to form tumors. In addition to this the hereditary transmission is unquestionble."

"The hereditary epidermal growths and fibromata are tumors developing directly from certain tissues and do not suggest any dyscrasia foundation."

"The other members of the class of hereditary growths make their appearance after birth on longer or shorter intervals. To this class belong the hereditary growths of the mammæ, uterus, skin, stomach, lymphatic glands and lung and are often seen in many generations of the same family; *e. g.* tuberculosis, syphilis, cancer, etc. But these are only predisposing causes. It is the predisposition which is inherited, not the disease."

"It is, however, certain that these growths appear at certain periods, such as the menopause or the beginning of menstruation; in such cases we must conclude that there exists in the tissues a certain weakness by which they are unable to adapt themselves to the disturbance which certain changes in the life processes entail, and that there is undoubtedly some organic condition or incomplete development. This condition is illustrated by the fact that certain tumors (keloids, etc.,) recur in the same cicatrix, and that a cicatrix is generally a tissue not mature and cannot compare in point of completion with the tissue which it ought to replace. Nævi are congenital irregularities and at later periods can develop into malignant growths." * * * * * * *

"We also know that on mucous surfaces tumors occur for the most part in such places where there previously was a simple inflammatory disturbance; *e. g.* where the simple inflammatory hyperplasia of chronic catarrh precedes the growth of polyps, and polyps may develop into cancer. In cancer of the stomach there is always seen a gradual transition of the catarrhal products to carcinomatous structure. Exostoses, warts, elephantiasis are all preceded by inflammation. We next come to certain regions of the body which, from their situation and the character of their function, are exposed to irritation and injuries. This renders them especially predisposed to take on a diseased nature; *e. g.* the stomach, sexual organs, bones, skin and the different orifices. If we make an estimate of all malignant growths we find that most occur at orifices and at the orifices which are exposed to the greatest injury, consequently those of the digestive and sexual apparatus are most affected."

"We know that certain organs are peculiarly predisposed to take on certain diseases, for, in following the history of a tumor we must come to the conclusion that in the tissue where the tumor exists there was some local predisposition. We know that not all kinds of tumors can develop in all organs. They have their favorite seats, certain tumors are seldom found in certain organs, while tumors found in one organ are seldom found in another. There must be something in the normal anatomical build which determines its mode of development. The same is true of secondary growths. In the testicle we frequently find secondary tubercles, but very seldom secondary carcinoma. We may say that nearly all those organs which are especially predisposed to primary growths, exhibit very little predisposition to metastasis; conversely we find metastasis most frequently in the lungs, liver, kidney and serous membranes, and just these parts are least prone to become seats of primary growths. The skin, mucous membrane, eye, nose and testicle are the common seats of primary growths and are seldom the seats of metastatic growths. The lymphatic glands, brain, muscle and bones stand between the two groups. The lymphatic glands are prone to metastasis and also to

primary growths, bone, to primary growths, being frequently the seat, also, of metastasis." All these facts together lead Virchow to the conclusion that even in malignant growths the primary growth does not come from a dyscrasia, and that every tumor is local and frequently of inflammatory origin.

These are the doctrines generally adopted, doctrines for which Virchow alone receives credit; but if we look through the older literature and even through the native literature of America we shall find a book written twenty years before Virchow's time, in which those fundamental ideas concerning tumors are set forth in all their essential points. I have reference to Prof. S. D. Gross's work: *The Elements of Pathological Anatomy*, published in 1839. I shall quote only a few sentences. "Tubercle," Prof. Gross says, "is always the result of inflammation and that this is the case likewise with scirrhus, seems sufficiently evident from what has been stated in regard to its exciting causes. Very frequently, it is true, the disease arises imperceptibly without local injury or obvious constitutional derangement. But this certainly does not prove that inflammation is not concerned in its production. How often do we find traces of inflammation after death, without having had the slightest indication of it during life? The fact, then, that inflammation is not manifested always by the usual phenomena, does not invalidate the idea of its presence." In another place he says: "Predisposition must also be accounted for and, in some instances, it seems to be connected with a hereditary taint, being transmitted from parents to their offspring." Hence he believed in the local inflammatory origin of tumors and conditions which predispose to them.

Dr. Woodward, U. S. A., in his excellent paper on the structure of cancerous tumors[1], agrees also with Virchow, saying: "The origin of the first growth was always to be looked for in local influences. Former injuries of one kind or another could be affirmed in a large number of cases to have preceded the development of the disease, and, though frequently the patients had lost all recollection of the original harm, yet it was in this

[1] Toner Lectures, Washington, 1873.

direction we ought to look rather than seek to explain away the real difficulty by invoking the aid of an imaginary cachexia."

Although Dr. Woodward at another page says: "The time has not come yet for any one to tell why cancer originates," he must be classed with the authors of the inflammatory theory of tumor formation, as he expresses the view that cancer cylinders are largely formed from migrated white-blood corpuscles; the latter when infiltrating tissues being always of inflammatory origin.

Samuel, of Konigsberg[1], although agreeing with Virchow in all the essential points, maintains more strongly than anybody else the view that inflammation is the main cause of tumors. He says: "The idea of excluding or even limiting the causative relation of chronic inflammation to neoplasms leads far astray from the right path."

The main reason for this view of Samuel is obvious. Like Virchow he cannot conceive of the difference between permanent inflammatory products and tumors, and he classes the products of specific inflammation, *e. g.* gumma, tubercle, lupus, etc., with the tumors. He does not admit, however, any special predisposition, nor does he admit Cohnheim's embryonic misplaced or supernumerary cells[2], but simply proliferation of cells by a process similar to chronic inflammation; a mere intensified afflux of blood he does not think sufficient.

The formation of malignant tumors capable of metastasis depends, according to Samuel, upon the want of resistance of the surrounding tissues or the removal of resistance of a given normal boundary. The formation of all tumors he ascribes to mechanical or chemical irritation, direct disturbance, "tearing, stretching" of tissues. Tissue is formed above physiological want and limit. The consumption being overbalanced by the proliferation of cells, "from the excess of new-formed material arises the tumor."

Wagner, Birch-Hirschfeld, Cornil and Ranvier and Perls hold the views as propagated by Virchow in their essential parts. Of our American pathologists and writers on this sub-

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[1] Handbuch d. Alleg. Path., 1879.

[2] See Embryonal Theory.

ject, I think, we must include here Prof. Fitz, of Boston, and Prof. Tyson and Dr. S. W. Gross, of Philadelphia.

2. Dyscrasia Theory.

To avoid misrepresentation I will literally quote all the strong points of the authors of this view.

Rokitansky was the first advocate of this theory in its present state[1]. The ablest advocates of this doctrine are, however, Billroth and Sir James Paget.

Sir James Paget's views are best expressed in a "Discussion on Cancer" at a meeting of the Pathological Society of London[2].

He holds that cancer is analogous to syphilis, gout, scrofulosis and other blood diseases, and he says that the transmission of cancer accords perfectly with what we see in them, not with what we see in local disease. He believes in a constitutional peculiarity residing in the blood, and that any exciting cause, in such a subject, may call forth in him a cancerous growth. Paget says: "While inheritance in simple tumors transmits the tendency to growth in one special part or special tissue, the hereditary tendency to malignant growths is not attached to any one organ or tissue, but may break out anywhere (?). What is transmitted is, then, not a property of any part of the body, but of the body as a whole." * * * * *

"I must maintain, therefore, that all the grounds against holding that cancer is a constitutional disease, will hold as strongly against a belief in any disease whatever, being a blood disease."

Billroth[3] holds a similar view. He says: "While fully recognizing the exercise of observation and brilliant ideas by which it is attempted to prove the purely local disposition to development of tumors, I cannot consider the proof as at all convincing, but remain of the opinion that there is just as much a specific predisposition to the development of tumors as there is to chronic inflammation, with proliferation of the inflammatory new formation, with suppuration, with caseous degeneration, etc."

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[1] Rokitansky, Hand-buch, 1846.
[2] British Medical Journal, 1874.
[3] Surgical Pathology.

"I would remark," he says, "that in regard to primary tumors we may assume in many cases that there are also specific, so called internal irritations developing in the body itself." * * * * * * *

"For my part I find it just as allowable to assume a diathesis here as in scrofula, arthritis, etc.; that partly from unknown, partly from known causes of general nutrition and ordinary conditions of life, abnormal matters proceed, which have a specific irritant action on this or that part of the body, analogous to that of certain drugs. Lastly, if to this we add that the diathesis for production of tumors is hereditary, although not to such an extent as the chronic inflammatory diathesis, the doctrine of weakness localized in certain systems of tissue, or certain parts of the body, seems entirely untenable. There is certainly a local cause for the members of one family having large noses; in proportion to the face, they have grown larger than in other men, still the large nose of the father cannot descend directly to the son, it can only be inherited from the father through the spermatozoa, and there the original cause is to be sought; all peculiarities that descend by inheritance are unquestionably to be termed constitutional." * * * *

"I think that the original causes for the local requirements for the development of tumors must be sought in specific peculiarities of the individual organism; in the same way we speak of a scrofulous or tuberculous person, meaning the pathological race, as it were, to which the individual belongs." * *

"Tumors, like inflammatory neoplasms, result from irritation of the tissue; the difference in the cause lies: 1. In the specific quality of the irritation. Infection of healthy tissue about a tumor, neighboring lymphatic glands, etc., is considered sufficient proof of this. It is supposed that under some unknown circumstances this specific irritant may be formed locally.—(Rindfleisch). I think that, partly as a result of hereditary predisposition, partly from a developed tendency, that is, where there is a diathesis we may imagine the formation of materials in the fluids of the body, which shall have specific irritant action on one or other tissue. 2. Any, usually an inflammatory irritation, may excite a tumor if the irritated tissue is specifically disposed for the development of growths."

As a curiosity I would mention the following view.

John Simon[1] regards a cancer as a gland, as a newly formed secretory organ, which is designed to collect effete material from the juices of the system in the same way as the kidney collects the urea from the blood. If the tumor is opened by ulceration a true excretory organ is created and the dyscrasia is temporarily suspended. Regarding cancer from such a standpoint, extirpation would be just as injurious as extirpation of kidney. For by extirpation of such an elementary organ the individual would be exposed to danger, as the physiological condition which had been created to relieve the dyscrasia would be destroyed.

The benign tumors Simon classes as monstrosities. Of late, however, Simon[2] has given up the dyscrasia view altogether. However persistently Paget and Billroth may defend their old views, I do not think that anyone earnestly believes any more in the dyscrasia theory of even the malignant tumors. Paget himself admits that "cancer is eminently a disease of degenerated tissue."

Virchow properly remarks[3]: "If there would exist primarily a specific dyscrasia we would not have a single, primary tumor focus from which metastasis proceeds, but we would have tumor eruption in all possible places without any definite plan."

3. Embryonal Theory.

Cohnheim, of Leipzig,[4] holds rather an exclusive view. Regarding tumors as typical new-formations of embryonal origin, he classes them as malformations, forming a subdivision of "monstra per excessum" (monstrosities). In order to understand perfectly this view of the etiology of tumors it will be necessary to present a few details of his doctrine.

Cohnheim excludes from the group of tumors the cystic growths and all the products of simple and of infectious inflammation, as well as the simple hypertrophic products. He

[1] Simon, Text-book on General Pathology, London, 1850.

[2] See Simon: Discussion on Cancer, British Medical Journal, 1874.

[3] Virchow die Kr. Geschwülste, Vol. II., p. 252.

[4] Allegemeine Pathologie, 1877.

retains, however, in the class of tumors the group of dermoid cysts or Virchow's teratoms, using the well established congenital derivations of the latter as a basis for his hypothesis of the etiology of tumors.

Cohnheim is the most energetic advocate of the purely congenital origin of tumors and makes their origin depend upon "an anomaly," or irregularity in the construction of the embryo.

With his usual positiveness in assertions, he most emphatically denies the possibility of any other direct cause of tumors.

Traumatism and the different irritations can, according to him, give rise to hypertrophic and inflammatory products, but not to true tumors. He also denies positively an infectious origin of tumors (the products of specific inflammation being excluded by him) upon the ground that tumors are never communicated from patient to the surgeon, or from wife to husband; and on the ground of the many fruitless attempts of inoculation from man to animals, or from animal to animal.

He admits, however, that living epithelial cells transplanted into the skin or aqueous humor of an animal will temporarily proliferate, but they will disappear within two weeks by absorption without impairing the health of the animal, the result being an abscess and, ultimately, a scar.

Small particles of periosteum introduced by Cohnheim under the skin of animals and into the lungs of dogs and chicken, by means of the jugular vein, had a similar fate. The particles of periosteum increased in size, ossified, but ultimately disappeared.

I will have to refer to these experiments again, which, by the way, have been repeated lately by Henry Wile in the pathological laboratory of the University of Pennsylvania, giving entirely different results.

Cohnheim further denies that nervous and other influences stand in a causal relation to tumors. True tumors, according to him, cannot originate by virtue of any kind of interference; only one causal factor exists, viz., an "*anomalous embryonic arrangement.*"

Similar views had been so far expressed by other pathologists

in regard to the origin of the dermoid tumors alone. These have been proven by Lücke and others to be due to anomalous invaginations of the outer layer of the blastoderm during the formation of the structure of the eye, mouth, neck, the ovaries, the testicles, etc.

Cohnheim applies to all neoplasms a similar mode of origin. He explains the anomalous embryonic arrangement which forms the starting point and becomes the cause of tumors, by the following hypothesis:

He says: "In an early stage of embryonal development there may be undoubtedly produced more cells than are necessary for the construction of a certain part; so that a certain number of cells remain superfluous. Their number may be very small, but they possess great proliferating power on account of their embryonal nature. This must occur before the complete differentiation of the blastodermic layer and the formation of organs." This appears to him the easiest explanation, why, from such a misplacement, there occurs, not the overgrowth of a certain part of the body, *e. g.* giant leg, but simply a histoid tumor, *i. e.* it results in an excessive overgrowth of only one tissue of the part. The superfluous cell material may be distributed uniformly, or it may remain together in one place. In the first case. there will result a superfluous part of the system like supernumerary fingers, etc.

"A positive proof," he says, "cannot be given: but there are numbers of facts which render this hypothesis probable in the highest degree."

Here he enumerates inheritance of tumors, quoting the well known instances of congenital tumors in members of the same family and in different generations; again, the fact that children are frequently born with tumors; referring also to the histogenesis of dermoid cysts. "The congenital tumors form only the minority and our theory would be a weak one," he says, "if we would base it only on this last fact, but we do not expect always that the individual will be born with a tumor; we only demand the existence of a quantity of cells produced, above physiological requirements, from which the tumor may be developed."

"To promote the production of the tumor we do not need any nervous influences or any kind of excitation, but only and alone *need sufficient blood supply.*"

Cohnheim admits that irritation and traumatism favor the formation of tumors, but that inflammation is by no means necessary for their development, and that no true tumor can be formed unless superfluous cell masses be present. The hypothesis of undeveloped germs is warranted by many facts. The mammary glands, the testis, the ovaries and the hair follicles on the lips remain latent up to puberty, the latter, occasionally, begin to proliferate in women after the menopause.

The extraordinary growth of the muscular fibres of the uterus is referred by Cohnheim to the stimulus given by pregnancy, to cells which before were quiescent, and the frequent occurrence of myoma in the womb of sterile women, to the abnormal development of the same cell masses, when their growth would answer no physiological purpose.

The occasional occurrence of extra fingers and toes, proves the existence of more cells in those individuals than was needed for the normal organism.

All primary heterotopic tumors Cohnheim supposes with Lücke and Waldeyer to be caused by aberrant cell masses; so the adenoma of the axilla, by the development of misplaced cells, cut off from the mammary gland; chondroma of the parotid, to those properly belonging to the ear; chondroma and osteoma of lungs to those from the ribs.

Both Cohnheim and Virchow have noticed cartilaginous islands in the shaft of adult bones, which, being according to Cohnheim supernumerary, may be inferred to give rise to the development of chrondroma and osteoma commonly met with in these parts.

Cancers are known to occur very commonly at the orifices of the alimentary canal, *e. g.* on the lower lip, cardiac and pyloric ends of the stomach, rectum, etc. Cohnheim offers an explanation by his hypothesis, to wit, that every such locality has been the seat, in the embryonic life, of some anomaly in development, such as the deposit or aberration of surplus cell masses which, if excited by excessive blood supply, will develop into a tumor.

Germs may fail to develop on account of the lack of necessary stimulus, or because of the resistance of surrounding structures.

Epstein[1] is a decided believer in Cohnheim's embryonal hypothesis. Having discovered epithelial pearls in the mucous membrane of the gums, the tongue and the genitals of newborn infants, he thinks to have found a proof for Cohnheim's view, regarding these pearls as the famous supernumerary embryonic collections of cells. These having no physiological purpose may either disappear, or under certain condition of nutrition form the starting point for tumors.

Prof. Maas, of Freiburg[2], declares himself strongly in favor of Cohnheim's theory on the etiology of tumors. He rejects positively all other theories, admits, however, traumatic influences in a greater extent than Cohnheim does. He even thinks that an injury frequently induces the development of tumors, but only in such parts where supernumerary embryonic cells exist. He says that only in such places containing those supernumerary cells an injury will react, starting a tumor by a "tumor-producing proliferation of cells"; while an injury inflicted upon a part where the cells are normal, will never produce that effect. By this hypothesis he tries to explain why thousands of injuries are not followed by the formation of tumors, while in a few instances tumors develop promptly in consequence of a trauma, and this only because in these few instances there must have been present abnormal embryonic cells which gave rise to the development of the tumor.

Hence he thinks that even a traumatic theory of the development of tumors, can be established only by Cohnheim's hypothesis.

He quotes several cases where nævi and other congenital formations developed into cancers in consequence of an injury; the latter, however, not being necessary in the presence of the numerous cases of congenital growths on record, and the large quantity of cases of tumors in which a traumatic history cannot be traced.

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[1] Epstein, Ueber Epithelialperlen, etc., Zeitsch. für Heilkunde, I., 1880.

[2] Maas: Zur Etiologie der Geschwülste, Berliner Klin. Wochenschr., No. 47, 1880.

Hasse[1] in an elaborate paper strongly approves the views held by Cohnheim.

F. W. Zahn[2] claims to have determined experimentally that portions of embryonic tissues engrafted upon animals continued to grow, while all other transplanted tissues of adult animals disappeared sooner or later. (See experiments.) These results if correct, would be in favor of Cohnheim's theory. Cohnheim's theory is certainly a highly interesting and ingenious one, and not without foundation, though some points are evidently exaggerated. For very able critics of this view see: Samuel[3], Lang[4], Osler[5], McGraw[6]. I am sorry to say, though, that some of the gentlemen did not read Cohnheim carefully and probably unintentionally misinterpreted and misrepresented his views.

Thiersch and Waldeyer[7], though not advocating so decided the embryonal hypothesis, are yet strongly in favor of it.

Lücke[8] believes in the purely local origin of all tumors, and defines a tumor as a simple multiplication of tissue above physiological limits. "It is interesting to remark," he says "that multiple warts may persist during the whole life of the individual; if, in advanced age, one of the warts should develop into a carcinoma, this transformation will nearly always be limited to such a single wart. Could this be the case, if we take dyscrasia as an etiological basis?"

Lücke says: that tumors of all kinds, even the most malignant ones and of considerable size before becoming general, may for a long time be latent in the organism without impairing the latter, if the local conditions are otherwise favorable.

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[1] C. Hasse. Die Beziehungen der Morphologie zur Heilkunde, Leipzig, 1879.

[2] Zahn, Sur le sort destissus implantes dans l'organisme. Congr. Med. International, Genéve, 1878.

[3] Samuel, Pathologie, l. c.

[4] Lang, Wiener. Med. Presse, 1879.

[5] Osler, Canada Med. and Surg. Journal, 1870.

[6] McGraw, T. A. The Germ Theory of the Etiology of Tumors, Detroit Lancet, 1878, p. 803.

[7] Waldeyer, Volkmann's Sammlung Klinischer Vorträge, No. 33.

[8] Lücke, Pitha und Billroth, Handbuch der allgemeinen und spec. Chirurgie, "Geschwülste.

Primary multiplicity is peculiar only to benign tumors. But there does not exist a lipomatous or fibromatous dyscrasia.

Lücke admits our great ignorance in regard to the etiology of tumors rather than accept names like dyscrasia, which are only used as a cloak for our ignorance. He, as mentioned before, admits the embryonal theory and believes in an individual predisposition, and to this he thinks should be added hereditary disposition and general and local circumstantial causes of various kinds, considering along with the latter, also traumatism.

4. Idiopathic or Spontaneous Theory.

Rindfleisch, in his famous text-book on Pathological Anatomy, expressed himself decidedly in favor of a spontaneous origin of tumors. His classical phrase: "Tumors arise spontaneously, but they do not heal spontaneously; while inflammations do not arise spontaneously but they heal spontaneously"—expresses really very perfectly the notion of the practical physician. The persistence, the "organ-like character of tumors," he explains by the fact that tumors follow more the rules of physiological growths. Inflammatory formations on the other hand are produced essentially by a conflux of mobile cells at the spot of irritation, hence their rapid appearance and almost traceless disappearance.

Rindfleisch[1] considers the evolution and involution of tissues and organs to be an important factor in the etiology of tumors. Thus, he explains the development of tumors of the connective tissue group by a localized, excessive proliferation of connective tissue elements during evolution (in young persons), and the occurrence of epithelial new growths during involution (in older persons), by a local proliferation of the superabundant epithelial elements. He admits, though, that local irritation plays an important role.

Thiersch's[1] hypothesis for the etiology of cancers is, that in advanced age, there occurs in the elements of the skin a dis-

[1] Rindfleisch, Handbuch der Gewebelehre, 1875.

proportion of the epithelium and the connective tissue, the latter losing its resisting power towards the epithelium, which proliferates, responding to given irritation. Some tissues, he says, become prematurely old. Benign moles and warts may begin to proliferate in advanced age and form malignant tumors.

Dr. Charles B. Nancrede[1], in his excellent paper, ascribed the cause of the formation of morbid growths to a disproportion in the local, vascular supply, in some points in accordance with the views of Thiersch[2] and Rindfleisch. Dr. Nancrede believes that the so-called inheritance of a cancer consists in the relatively earlier atrophy of the connective tissue and the transmission, from father to son, of a peculiar readiness to respond to irritants of the glandular elements. As to the exact nature of the irritation which sets up this abnormal action, he believes that there is, in all cases, some slight mechanical or chemical irritant acting upon the "*locus minoris resistentiæ*," anatomically prepared for the morbid growth, and he defines this irritant not as a violent blow or a cauterizing agent, but anything that increases the amount of blood in the part, however unnoticed or unnoticeable it may be.

In connection with the idopathic or spontaneous theory due notice must be given to the views of Mr. Payne[3], who applies Spencer's dynamical laws to the causation or rather to the growth of tumors.

Herbert Spencer says: "Growth is unlimited or has a definite limit according as the surplus of nutrition over expenditure does or does not progressively decrease. Tumors, having no function, have no expenditure, and hence all the force is used up in growths, and the larger the tumor the more force is liberated and the larger it grows. They are like plants in being almost wholly accumulators; they have no expenditure of force, hence their unrestrained increase in size."

Mr. Payne properly remarks: "New growths are more frequent in passive tissues than in actively functionating tissues. Fatty tissues, bone tissues and all varieties of growths which

[1] Nancrede, Transaction of the Pathological Society of Philadelphia, 1876–7.
[2] Thiersch, Der Epithelialkrebs. Leipzig, 1865.
[3] Payne, Origin and Relations of New Growths, Brit. Med. Journal, 1874.

originate from connective tissue, are instances of the connection of mechanical passivity with excessive growth." On the other hand, he explains the extraordinary rarity of tumors composed of striated muscular tissue by the strong activity of the latter, the nutritive supply being balanced by the expenditure of force.

S. Stricker[1], of Vienna, expresses no views of his own on this subject, but it appears that he is inclined to believe in the spontaneous origin of tumors.

5. Nervous Theory.

A nervous theory of the etiology of tumors is also more or less ably advocated. I will briefly mention the arguments brought forward:

Schrœder Vander Kolk[2] after cutting the tibial nerve and breaking the bones of a dog's paw, found that instead of regular callous forming, a tumor grew resembling a medullary cancer. Hence he ascribes the development of a tumor to want of innervation.

Virchow says, however, that almost the same tumor can be produced by breaking the lower jaw of a rabbit just in the median line where there are no nerves. Many experiments of nerve section with fracture have been tried, but without success.

Lang[3] advocates a purely nervous theory for the etiology of tumors. He argues as follows: "I find that the relation of the nervous system to tumors is very much underrated by some and by others altogether ignored, yet to me it seems in many cases very probable." * * * * * * * * * * *

"There can be no doubt now that lesions or diseases of nerves or their centres are the results of decided disturbance of nutrition and that these, in several cases, give rise to increased formations of different kinds: connective tissue hypertrophy, hyperostoses, hypertrophy of the whole side of the face, etc. * * * * * * * In all these cases I place the

[1] Stricker, Vorlesungen in der allgemeine und experimentelle Pathologie, II, 1878.

[2] Quoted by Virchow, Krankhafte Geschwülste.

[3] Lang, Wiener Med. Presse, Nos. 16, 18, 20, 1879.

origin of the diseased condition in the nerve centres, whence it proceeds towards the periphery along the course of the nerve creating disturbance." * * * * * * * "Not unimportant appears to me in connection with the observation made lately by Billroth[1] and Esmarch, that malignant tumors are caused to disappear entirely by the use of internal medicine. As the most important remedy to bring about the effect is arsenic, and it is this drug that relieves the most desperate cases of neuralgia."

"That arsenic affects as an alterative the organism and brings about a favorable condition in the processes of nutrition, the dermatologist has ample opportunity to observe. Exactly the physiological process in which it acts is yet unknown, but we may suppose that it acts upon the nervous system or that part called trophic nerves which control nutrition. From experiments on animals we find, that arsenic does not enter all organs with the same degree of readiness, but that it enters some much more readily than others. The organs most disposed to take it are the brain and spinal cord."

"Scolosuboff[2] therefore, advises in criminal cases for poisoning by arsenic, to examine the brain, likewise in cases of gradual arsenical poisoning. Hoffman[3] and Ludwig obtained the most pronounced arsenical mirrors from preparations of the brain and liver."

In respect to the possibility of the dependence of the development of tumors upon the central nervous system, Lang makes the following concluding remarks: "It is conceivable and possible to conclude, and by analogy from other processes, it is even probable that if the disturbances of nutrition are controlled by trophic centres, the first impression coming from the periphery, the disturbance of nutrition may exist as the result of a reflex. Regarded in this light we can explain the success of the dietary treatment of cancer; for, Beneke and Esmarch[4] found that when the peripheral terminations of nerves

[1] Billroth and Esmarch, Wiener. Med. Wochenschrift, 1871.
[2] Scolosuboff, Jahresbericht der Chemie, 1875.
[3] Hoffman and Ludwig, Wien. Med. Jahresbücher, 1877.
[4] Beneke and Esmarch, Langenbach, Archiv. vol. 22.

of the alimentary canal are less irritated, disturbance of nutrition is less likely to occur from reflex action. Individual peculiarities must, however, be taken into consideration, as we know from experience various articles of food have peculiar effects upon the nerve termination of some individuals, and the direct relation of cause and effect can be observed; *e. g.*, where strawberries, lobster, ham and other articles of food produce urticaria in some persons."

Beneke[1] himself, however states, that he does not think that the nervous system is in any way influenced by the dietary treatment in cancer.

Dr. Snow[2], of London, in his paper on the etiology of cancer, based upon two years statistics from the cancer hospital, comes to the conclusion that nervous depression, especially mental trouble, is the most prominent cause of cancers. He says: "Of 103 uterine cases in which preceding causes of mental or physical nervous depression (trouble or very hard work) were sought for, 55 gave a history of previous mental trouble, 15 of hard work alone, while ten gave doubtful replies. Of 38 breast cases, 24 patients gave a history of sorrow and anxiety, 4 of hard work, while 1 was doubtful. Thus of the breast cases, (although I must confess the number specially investigated in this connection is smaller than I could wish) 73.68 per cent, gave an account of nervous depression, either mental or physical, immediately preceding the appearance of the disease, while in the uterine cases the percentage amounts to 63.1. From this I cannot help inferring that sorrow, anxiety and hard work are very powerful factors in the production of malignant disease."

After careful inquiry into the history of a large number of cases, he comes to the following conclusions:

"1. Hereditary tendency, as a predisposing cause of cancer (at all events of mammary and uterine), is almost valueless if not entirely so, and in practical diagnosis should altogether be ignored as misleading.

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[1] Beneke, Berliner Klin. Wochenschrift, No. 47, 1880.

[2] Snow, London Lancet, Dec. 1880.

2. Mechanical injuries directly produce cancer in a certain percentage of cases, but this percentage is small.

3. As direct and immediate causes of cancer, (especially in my own experience of uterine cancer) mental trouble, hard work are very potent agents, and exert more influence than any other antecedent within our present knowledge.".

II. EXPERIMENTS.

Positive science rests upon facts as deduced from experiments and through experiments and the microscope only can the true nature and the etiology of tumors be settled. As yet very little has been done in this line, and the results of experimenters hitherto pertain only to the inoculability or infectiousness of tumors.

On account of a discrepancy among authors as to whether tumors can be inoculated or not, and on account of the different interpretation which they ascribe to the experiments done, I find it necessary to quote all of them and to show why certain experiments succeeded and others failed.

It seems to me that the main object the experimenters had in view was to find a specific virus in tumors; the nature of the experiments and the results seem to justify such an inference. Furthermore the experiments have an important bearing on the etiology; for this reason, also, it will be necessary to review them before entering upon a *resumé* of the etiological facts.

Infection certainly may take place in the same individual by metastasis, but whether it takes place from one individual to another is disputed. The products of specific inflammation, viz., gumma, tubercle, lepra, etc., are not included here. There is only one positive statement on record, that of Eiselt[1], who, in the case of a man suffering from melanotic tumor, asserted that the patient had been infected from horses. In rare cases it has been observed that an ulcerating tumor infects by contact a structure which merely rests or lies upon it.

Lücke had observed the buccal mucous membrane to be in-

[1] Prager Vierteljahrschrift, 1861, Vol. 70.

fected by contact from an ulcerating cancer of the tongue and to become the seat of an independent cancer. He also directs the attention to the frequent occurrence of cancer in Douglas's pouch, secondary, by direct contact, to cancer of the abdominal viscera.

a. Experiments: Negative Results.

The first experiment on inoculation of tumors is carefully recorded by Peyrille in his Latin dissertation in 1774[1]. He injected under the skin of the back of an animal some juice from a cancer of the breast and thought that on the fiftieth day there was produced a cancer. But from his own description it is probable that the process was rather one of pyæmic nature, as Dr. Zahn relates.

Dupuytren, Valentin and Vogel, in their time, also experimented with tumor inoculations upon animals, making injections with "tumor juices or with minutely pulpified tumor particles," but with negative results.

Gohier[2] records that inoculation of horses, asses and dogs with melanotic tumors have not been successful in his hands.

Virchow[3] mentions that he introduced, without success, into wounds of the skin and the conjunctiva of rabbits and dogs fresh melanotic sarcoma of man.

Billroth did not succeed in inoculating the ears of a rabbit with juice of a melanotic sarcoma from a man.

Hyvertl,[4] desirous of ascertaining the effects of cancer grafts upon the body of rabbits, undertook a series of experiments. The portions of tumor, free from pus, and not far advanced in development, were introduced deep into the tissues as far as the muscular layer. Inflammation and induration resulted, the latter to be felt five months afterward as a "tumor." This was surrounded by a tissue rich in vessels, and presented its previous appearance: cancer-cells and alveoli at the periphery with granular degeneration at the centre; at the latter point

[1] Quoted after Zahn, Congrés International Médicale, 1877. Geneve, 1878.
[2] Gohier Memoir, p. 338.
[3] Virchow, Kr. Geschwülste, Vol. II., p. 253.
[4] Hyvertl, Gaz. des Hôp., No. 49, 1873. Allg. Med. Centr. Zeit., 1873, p. 602.

was calcification. The autopsy showed that neither infection nor general disease resulted. The author concludes that young cancer-cells, transplanted from man to animals, do not produce cancer.

Lang,[1] impressed by the idea that heterotopia of cells or tissues gives rise to tumors, undertook a series of experiments, introducing various tissues into different parts of animals; but, in his eagerness to be judicious, he actually destroyed the tissues before introducing them, as can be seen from his own account.

The experiments were made on thirteen dogs, varying in age from a few days to several years. He used either normal tissue or such as had been in an inflammatory condition, introducing it either into the organism of the same dog, from which the tissue was taken, or into other dogs. For this purpose he rendered the tissue to be introduced as fine as possible on a plate, warmed to a temperature of 38° C. He then suspended the pulp in a 12 per cent. solution of carbonate of sodium, of the same temperature, and introduced it into different parts of the animal by means of a hypodermic syringe.

Such experiments Lang carried on with skin, glands of skin, mucous membrane, mucous glands, the nipple of the breast, the mammary gland, cartilage of the ear, joint epiphyses, and with young bone-tissue. All these tissues, prepared as above stated, were introduced subcutaneously seventy-seven times; five times near the bone; twice into the substance of the mammary gland; once into the testicle; forty-three times into the peritoneal cavity; three times into the thoracic cavity; twenty-three times into veins, and eleven times into arteries; in all there were one hundred and sixty-five experiments.

Out of the thirteen dogs, which had been experimented upon, six ran away and some died and seven were under his observation for some time; yet no tumors developed.

Zahn[2] transplanted fragments of chondroma into the anterior chamber of the eye, without success.

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[1] Lang, Die Aetiologie der Malignen Geschwülste, Wiener Medicinische Presse, 1879, No. 16.

[2] Zahn, l. c., p. 633.

b. Experiments: Positive Results.

Langenbeck[1] injected fresh cancer juice into the jugular vein of animals. Many of them died in from twelve to twenty-four hours, the juice forming so great an obstruction in the lungs that they all died of dyspnœa. One experiment was performed upon a large, strong, two years old dog. He first took from the femoral artery eight ounces of blood, injected a half ounce of cancer juice (taken from a growth two and a half hours after removal), mixed with defibrinated blood, and all was injected into the femoral vein; two days after the operation the dog had a fever and dyspnœa; eight days afterwards the dog was well, but began to get thin; three months later the animal was killed; in the lung was found three flat nodes, which, under the microscope, proved to be cancer.

Virchow, who examined the microscopic preparation, agrees with the diagnosis of Langenbeck, but remarks that it fully resembled congenital cancer of dog.

Klencke[2] succeeded in inoculating a horse and a dog with a melanotic tumor from another horse.

C. O. Weber[3] injected some cancer juice from a medullary cancer of man into the cruval vein of a dog, and also introduced particles of the tumor under the skin; at the end of sixteen days a tumor of the size of a fist was formed beneath the skin, having the structure of a true medullary cancer.

Follin and Lebert[4] injected cancer juice from a mammary carcinoma into the jugular vein of a dog, and in fourteen days cancer-nodes were produced into the heart and liver.

Goujon[5] testifies to have successfully inoculated animals with cancer masses three times in four experiments.

Lebert and Wyes[6] record the following experiments: 1. juice of melanotic sarcoma introduced under the skin of the neck of

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[1] Schmidt's Jahrbücher, vol. XXV, 1840, p. 99.

[2] Klencke, Häser's Archiv., 1843, vol. IV.

[3] C. O. Weber, Chir. Erfahrungen und Untersuch., Berlin, 1859, p. 259.

[4] Follin and Lebert, Traite practique des maladies cancereuse, Paris, 1851, p. 136.

[5] Goujon, Etudes sur quelque points, etc., These, Paris, 1866.

[6] Lebert and Wyes, Virchow's Archiv., XL, pp. 142–532.

rabbit was followed by death in two and a half months; at the point of injection, in its connective tissue, appeared a pigmented sarcomatous mass, made up of tubers in all two inches square. Internal organs sound.

2. Rabbit injected in neck with juice of melanotic sarcoma; killed in three and a half months. In connective tissue, at point of injection, a pigmented zone, three centimeters long, two centimeters broad. Suppurative pleuritis; but viscera sound.

3. Three rabbits injected with the juice of small round cell sarcoma of the tibia of a man; no results either local or general.

4. Four rabbits were injected with juice of human carcinoma; no results.

5. Injected from 60 to 70 grammes of juice of carcinoma of heart into jugular vein of a dog; death in fourteen days. In the heart a number of small nodules of carcinoma and miliary carcinosis of liver.

Dr. Eiselt[1] says that Prof. Klencke of Braunschweig, inoculated the conjunctiva and lachrymal gland of an old horse, with juice of a melanotic tumor of orbit. In sixteen weeks the entire gland was involved by a similar tumor, causing eye to protrude. Introduced fragments of same tumor into jugular vein of a dog, which died in three months, melanotic tumor in left lung.

H. Knapp[2] made inoculations by injections under the skin, and the crural vein of a rabbit and dog with glioma of the orbit; failed. He succeeded, however, in obtaining increase of bulk of tumor-particles, introduced into the vitreous body of the eye which, while increasing, retained their glioma structure.

The author thinks it possible, however, that the new products (which probably had been adherent to the choroid) may have been of inflammatory nature.

M. Nowinsky[3], who experimented in the laboratory of Prof.

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[1] Dr. Eiselt, Prager Vierteljahrschrift, Bd. 76, 1862, p. 53.

[2] H. Knapp, Weber Imphungen von Gliom-gewebe vom Menschew auf Kaninchen und Hunde Verhandl. d. natur. his. und. med. Ver. Heidelberg, 1868, IV, quoted Medicin. Centralblatt., 1869, p. 79.

[3] M. Nowinsky, Med. Centralblatt, 45, 1876.

Wowontzoff in St. Petersburg, asserts that cancer can be inoculated. He used for inoculation small fragments of a medullary cancer taken from the nose of a dog. Twelve experiments were made on inflamed skin; fifteen experiments were made on normal skin. The first were all negative; out of the second two were positive. One of these was as follows:

On the back of a dog a fresh cut was made and a small piece of cancer, 2 c. m. m. in size was introduced and the cut sewed up. It healed by first intention; after fourteen days there appeared in the cicatrix a small nodule, of the size of a pea, which seemed to grow very fast, so that eight months after the inoculation, the growth was as large as a walnut. Superficially it had been ulcerated; a month later the dog was killed; the tumor 3½ c. m. in diameter, soft, and on section white. In the subclavicular region a gland was very much swollen. The microscope showed the tumor to be made up of epithelial cells infiltrating the connective tissue. In some places the cells were arranged in alveoli. The lymphatic glands showed metastatic cancer masses. Thus the new-formation had the same structure as the tumor, a piece of which was used for inoculation.

In the other case a piece of the small nodule from the first dog that was inoculated, was put into a young dog three months old, which died one and a half months after inoculation from malignant pustule. There was found in the cicatrix a small nodule of the size of a pea; no metastasis. The microscope revealed carcinoma.

A series of experiments of the same character as the foregoing is being carried on at present in the Pathological Laboratory of the University of Pennsylvania by Henry Wile. It would be premature to dwell upon them now, as they are yet in progress. The first series of experiments undertaken by him with injections of cancer juice, failed in every instance. In the second series, so far, of a number of dogs upon which small fragments of carcinoma of man were transplanted subcutaneously, only two have distinct new-formations at the seat of the grafts, one of them being of the size of a walnut; the lymphatic

glands in the axilla and groin are swollen. The animals will be kept alive until January, 1882. The structure of these new-formations is unknown. It was, however, perfectly determined in a third animal (a small dog) that a cancer-graft continued to grow and, retaining the typical structure, reached a ten-fold size within two months, when the animal was killed.

In a large number of animals, however, the transplantation failed. The details of the research will be published when completed.

Analyzing the results of the experiments, it is seen that tumors were developed only in those cases where direct transplantation with living fragments of tumors had been made. In no case where tumor-juices were injected were any tumors formed; but at the most, perhaps, only a miliary infiltration of a new growth. Langenbeck's experiments, in which the injection of juice appears to have been followed by the formation of a tumor, was the only exception to this.

The juices as occurring in malignant tumors are always the products of degeneration of the tissue or cells composing them. The cells suspended in that juice are dead, having undergone fatty or some other degeneration, and this is the reason that injection with juices fails. If the particles of living tumor-tissue in which the relation of blood-vessels to cells is preserved happen to be suspended in that juice, "inoculation" might succeed.

c. Other Transplantation Experiments.

Paul Bert[1] asserts that any tissue, with the exception, perhaps, of muscle, can be successfully transplanted.

Gonjon[2] showed that young marrow of bone can be transplanted with success. He also found that the transplantation in very vascular tissues is particularly successful. The experiments were successful only with tissues of the connective-tissue group and only if transplanted upon animals of the same species whence the graft tissue was taken; otherwise the tissue experimented with was eliminated promptly by inflammatory

[1] Paul Bert, quoted after Zahn.

[2] Gonjon, l. c.

suppuration or was atrophied, becoming encapsuled in inflammatory connective tissue.

A number of successful experiments of transplantation into the anterior chamber of the eye were made by Dooremal[1] with mucous membrane of the lip; by Goldzicher[2] with that of the nares and the conjunctiva and with tissue from the fallopian tube; Schwenniger[3] with roots of hairs. All these experimenters found that particularly the epithelium proliferated and occasionally formed masses of new-formations and cysts. Experiments with corneal and nervous tissue gave negative results. Montegazza inserted various tissues into the peritoneal cavity and beneath the skin. He obtained positive results with bone tissue, testicle, spleen and intestines, *i. e.* the tissues grew at the seat of transplantation.

Zielonko[4] transplanted various tissues into the dorsal lymphatic sac of frogs; he succeeded only with corneal tissue and even here only the deeper, younger cell-layers proliferated.

Zahn[5] made transplantation experiments on rabbits. Rabbits proved, for these experiments better than other animals, and the best results attended transplantation to the anterior chamber of the eye and the kidneys. He experimented, however, only with cartilage. With fragments of costal cartilage from adult animals, even when transplanted to animals of the same species, he always failed. He introduced several tissues, fragments of an enchondroma, into the anterior chamber of the eye and into the circulation, but, like other adult cartilage, they invariably underwent fatty degeneration and were absorbed.

Zahn then began to experiment with fœtal cartilage and always succeeded. The fragments of cartilage continued to grow though they occasionally calcified in their interior. On one occasion he injected into the circulation cartilage so minutely divided and mixed with amniotic fluid that it could pass

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[1] Van Dooremal, Graefe's, Archiv., Vol. XIX.

[2] Góldzicher, Arch. f. Exper. Pathologie, Vol. II.

[3] Schwenniger, Zeitschr. f. Biologie, Vol. XI.

[4] Zielonko, Med. Centralblatt, 1873, No. 56.

[5] Zahn, Sur le sert des tissus implantés, etc., Congres Méd. International, Genève, 1878.

through a capillary tube of a hypodermic syringe. At the end of fifty days he found two cartilaginous nodes, one of them of the size of a pea, in the adventitia of a vein. He succeeded also in transplanting fœtal cartilage from one species of animal to another, *e. g.* from a cat to a rabbit, which shows that the same fœtal tissues of different species of animals are equivalent.

Zahn says that the same results are obtained after experimenting with fœtal bone. He adds: If an entire fœtal organ is transplanted, *e. g.* a femur, it continues to grow, retaining pretty nearly its forms though it accommodates itself to the shape to the organ into which it is introduced. One of these transplanted femurs Prof. Zahn exhibited at the International Medical Congress in Geneva. "Upon its diaphysis there was developed an exostosis, and on its epiphysis some enchondromata." Zahn did not think that his results in the transplantation of tissue deviated much from those of others. Other reliable experimenters succeeded in transplanting only those tissues which contained some young developing or germinating cells or cell-layers, such as red marrow of bone, the roots of hairs and periosteum of young animals. Nobody probably succeeded in transplanting nerve and muscular tissue; "the practical surgeon," he says, "will not undertake a resection of bone in an old person in whom the periosteum has lost its osteogenetic properties." Virchow[1] thinks very highly of Zahn's experiments and considers that his results solve the problem of the transplantation of tissue.

In connection with this it is also interesting to read Ball's[2] monograph which, however, does not contain anything new.

Cohnheim and Maas[3] undertook some experiments to determine whether a piece of periosteum would grow and develop bone in the lung, being introduced by means of the jugular vein. Experiments were made on rabbits, dogs and chickens, always taking young subjects. The best results were attained with chickens. In from three to five days the ani-

[1] Virchow, Archiv., Vol. 79, p. 189.
[2] Ball, Das Princip des Wachsthums, Berlin, 1876.
[3] Virchow, Archiv., Vol. 70, 1877, Cohnheim and Maas.

mals were killed; the embolus could not be detected on the external surface of the lung, but in ten or fifteen days it could be detected as a resisting and hard spot in the parenchyma of the lungs. In experiments, however, of twenty days duration the results were negative; the emboli had disappeared. In the first three or five days the periosteum thickens and is infiltrated with a large number of wandering cells, sometimes collected in masses; in ten to twelve days were found hyaline cartilage cells; in fifteen to sixteen days bone lamella were always found. From these experiments one would be led to believe that small particles torn off from parent mass were carried by the blood vessels, getting stuck, proliferated, and in this way a primary tumor gives rise to a secondary tumor. But the following experiments disproved this view: After twenty days the embolus could not be felt in the lung externally; on cutting open the artery the periosteum was found well shrunken together, and of ossification nothing was seen; after the lapse of a month not a trace of the embolus was found. It is just the same in subcutaneous transplantation; it grows for a while but soon becomes reabsorbed and disappears.

Cohnheim and Maas[3] argue now as follows:

It may be attributed to some physiological condition of the organism which, as in callus by fracture, throws out of the system all foreign matter. If this is right, then in those individuals who suffer with metastatic tumors, the ability of the organism to resist the introduction of foreign matter is wanting.

At my suggestion a number of experiments were made by Henry Wile, in the Pathological Laboratory of the University of Pennsylvania[1], to determine whether periosteum transplanted

[1] The work of Henry Wile is only one of the numerous experimental researches carried on at present by a number of students on different subjects in the Pathological Laboratory of the University of Pennsylvania. We are extremely satisfied with the excellent facilities for work in the laboratories of this institution, the ample supply of instruments and pathological material and so forth. Original research is liberally encouraged by the faculty and by the chief of the pathological department, Prof. James Tyson. Notwithstanding an endowment fund would be desirable for the purpose of publishing the works which are now being carried on and those which have accumulated during the last few years. So far, but very few of the latter are published and these only in short abstracts and insufficiently illustrated by wood-cuts. The objection to these papers by the edi-

under certain conditions would continue to grow and develop bone, or as Cohnheim says, disappear at the end of twenty days. With the permission of Mr. Wile, I will briefly give the essential points and the remarkable results of these experiments.

Six of these experiments have been selected and the results are as follows. Dogs were used in every case:

1. A small piece of periosteum from radius of an adult dog, was introduced into the right jugular vein. Dog was killed after thirteen days. In the right middle lobe of the lung near the surface was found a small resisting nodule which on section showed it to be made up of granulation tissue containing cartilage cells.

2. Periosteum introduced the same as before. Dog was killed after twenty days; a nodule found in right inferior lobe of lung somewhat larger than preceding nodule. On section under the microscope it proved to be made up partly of young cartilage and partly of well formed bone.

3. Periosteum from tibia introduced into right jugular vein as before. Dog killed at the end of thirty-three days; a nodule was found in right middle lobe of lung; this nodule was perceptibly larger than the one in the preceding experiment and was still found to be made up of bone tissue.

4. Periosteum introduced as in last experiment. Dog was killed at the end of thirty-seven days. A resisting nodule larger than in the preceding experiment was found in the right middle lobe; under the microscope it proved to be bone.

5. Periosteum introduced as before, and dog killed at the end of fifty days. A nodule was found in right middle lobe of lung of the size of a pea; it also proved to be bone.

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tors of American journals is their bulk, the cost of the wood cuts and plates, and occasionally that the contents are purely of scientific interest. Now these researches should not be published in a crippled manner and be lost in a host of most wonderful obstetrical and therapeutical curiosities, but should be issued in full, in separate periodical issues and all the best plates reproduced at any cost. In such form they would soon be noticed as worthy products of American histology and pathology, and may be sent to those members of the medical profession both here and abroad, or would be procured by those who are interested in scientific medicine. At the same time the proper publication of these works would be a further encouragement to students to engage in original research and thus to elevate their standard and that of their Alma Mater.

6. Periosteum introduced as before. Dog killed at the end of one hundred days; several hard nodules were found on the periphery of right lung, one of them being of the size of a large pea, *i. e.*, about one hundred times larger than the original particle introduced. Careful microscopic examination was made; result, bone tissue.

The microscopic diagnosis was confirmed by me in every case.

In each experiment it must be noted, that there was a perceptible increase in size in the periosteal embolus. These facts show positively that the periosteal embolus will not only not disappear at the end of twenty days, but under favorable conditions ossify and continue its growth and development indefinitely.

Hence there must be something wrong in the experiments of Cohnheim and Maas, and consequently all their conclusions drawn from them cannot be substantiated.

Cohnheim's hypothesis on the etiology of tumors seems of late to gain some more ground in Germany. While my paper was in press, the just issued (August 8th, 1881) part of Vol. 85, of Virchow's Archives reached my hands, which contains an article (Exper. Nutersuch ueber die Etiologie der Geschwülste) by Dr. Leopold, who violently supports, and thinks to have proven by experiments, the view of Cohnheim. I can give here only the mere outlines of the contents of the paper.

The author had made a series of transplantation experiments in Pathological Institute of Leipzig, under the direct supervision of Cohnheim. Essentially these experiments went only to confirm the experiments of Zahn (l. c.) e. g., that only embryonal (fœtal) tissues transplanted into the anterior chamber of the eye or into the peritoneal cavity will grow; while adult tissues do not grow but become absorbed sooner or later. Successful results Leopold obtained only with embryonal cartilage, transplanting small fragments into the anterior chamber of eye, where they continued to grow and in about six months reached a bulk three hundred times larger than the original pieces inserted. Larger pieces of tissues and organs, i. e., a whole fœtal head or a thigh inserted into the peritoneal cavity did, however, not grow even after the lapse of months, but were peculiarly preserved without decomposing, becoming enveloped into a connective tissue capsule. The fragments of cartilage referred to above had not only considerably increased in size but showed advancing development, viz.: the formation of marrow-cavities and of bone lamella.

From this the author concludes, that he has produced experimentally a tumor, an artificial enchondroma (?) He thinks that he will also be able "to produce artificially in the same manner epithelioma, myoma, adenoma and dermoids."

I think, however, that he must succeed better with them than with his "artificial enchondroma" which is nothing else than a simple graft of cartilage transforming into bone.

I must confess that Cohnheim's embryonal hypothesis is very seducing, but still it can hold good only for the congenital tumors, viz: Rhabdo-myoma, simple angioma and lymphangioma, dermoids, and perhaps the heterotopic adenomata. For all the rest of the tumors Cohnheim's theory is untenable, as will be shown later.

The results of all the experiments taken together may be summed up as follows:

1st. Tumors cannot be inoculated by virtue of a specific poison or of any specific properties.

2d. Fragments of tumors, when transplanted from one individual to another, continue to grow and may reach considerable size.

III. STATISTICAL FACTS.

Allow me now to enumerate briefly the main etiological facts as deduced from statistics and observations, arranging them somewhat after the pattern of Prof. Lücke, and to give some additional points, which are of interest in the etiology of tumors.

1. *Hereditary predisposition.* Broca in his Treatise on Tumors, p. 151, gives some interesting statistics. One of these is as follows:

1st generation, Madam Z. died, aged 60, from cancer of the breast.

2nd generation, four married daughters died at ages from 43 to 62 of cancer of liver and breast.

3d generation, one of these daughters had seven children.

1st son died young.

2nd son died, age 64, cancer of stomach.

1st daughter died, age 35, cancer of breast.

2nd, 3d and 4th daughters died, age 35 to 40, cancer of liver.

5th daughter remained free.

In analyzing the family still further it was established that out of a family of 26, in three successive generations 15 individuals died of cancer.

According to statistics given by Lebert,[1] the development of cancer as far as hereditary influence appears in a ratio of 1 to 7. Nearly all experienced authorities agree with this.

Other tumors, too, have been traced for several generations, either upon the same or upon different parts of the body.

Dr. Snow, of the London Cancer Hospital, Birket and Wilks

[1] Lebert, Traité practique des maladies cancereuses, Paris, 1851.

of London, and some others consider cancer not to be hereditary.

2. *Age* predisposes to tumors and certain ages to special forms of tumors. According to Virchow, the frequency of the occurrence of tumors in general stands in direct ratio to the age up to the 71st year.

In reviewing the predisposing and exciting causes of mammary neoplasms, S. W. Gross[1] arrives at the conclusion "that their development is connected with the changed proportions of the component tissues of the breast at different periods of life, and that the condition of the tissues is, as a rule, indicated by the age of the patient." He agrees with the opinion that the evolution and involution of tissues, as conditioned by age, plays an important role in the etiology of tumors. A "prematurely old breast," Dr. Gross says, is predisposed to carcinoma.

3. *Sex* predisposes to tumors. Statistics given by various distinguished writers show that neoplasms in general are more common in the *male* than in the *female*, with an averaging ratio of 6 to 4.

This ratio differs somewhat in the case of cancers.

4. *Certain physiological periods of life* predispose to tumors —e. g. adenoma—dermoid cysts.

Statistics show that marriage and menopose predispose women to tumors.

5. *Social conditions*, prosperity and good life predispose to tumors.

6. *Certain kinds of food* are supposed by some to promote the development of tumors, especially of malignant ones. It is said that predominately vegetable food predisposes to cancer.

Roll[2], giving an interesting comparative study of tumors in animals, states, however, that cancer is more common in the dog than in the herbiverous animals.

In the western portion of the United States there is a popular belief that tomatoes produce cancer. So much importance

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[1] Gross, S. W., Tumors of the Mammary Gland, Philad'a, 1880.

[2] Lehrbuch der Path. und Therap. der Hausthiere, Wien, 1860, p. 257.

was attached to this belief that the question was made the subject of an investigation by the Michigan State Board of Health, which, however, failed to establish any ground for this opinion.[1]

7. *Race.* It would be interesting to know whether certain races and nationalities exhibit any special predisposition for the development of tumors.

It is generally supposed, Lücke says, that people of the South are less predisposed than those of the North. It may be so for cancer and sarcoma; but it is well known that connective tissue growths (elæphantiasis) and Lipoma, in Hottentots, are found very frequently in the South. In negroes, tumors of the skin are very common.

During my visits to Egypt in 1868 and 1872, I was struck by the frequency of tumors among the native Arabs. Sometimes they were of considerable size and mostly, I think, located about the neck, face, axilla and lips, or multiple tumors in skin.

Their nature I do not know as I was not interested in medicine at the time. I failed to discover any records of tumors in those countries, except those which I will quote.

Dr. Fraue,[2] who traveled for many years in Asia Minor, Syria, Palestine, Mesopotamia, Egypt and Nubia, found that in these regions cancer especially and also epithelioma of the lip was almost unknown (?) also Dr. Heinrich Bartle, the famous African traveler, who made observations in these regions for a period of five years, states that he saw only one case of

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[1] This belief has been traced by Dr. Wyman to the following source: J. D. Hylton, M.D., Professor of an Eclectic Medical School, writes as follow in the *Eclectic Med. Journal of Penna.*, Sept. and Oct., 1871. I will quote here the article as an curiosity: "In my chemical researches in the vegetable kingdom I am daily discovering new agents. In the tomato I can isolate a pure alkaloid, which possesses chologogue properties superior to podophylin, leptandria, euonymous, mild and efficient in its action. But in my microscopical researches with this same agent I have discovered *cell identical with cancer cells, the appearance of the two, the true cancer cell and those found in the tomato, being under the microscope the same.*" The learned quack adds: "If this fact is true and can be substantiated by other chemists, it may in some manner account for the fearful increase of cancer in sections of the county where this fruit is cultivated." (!)

[2] Virchow's Archives, Vol. 25, p. 602.

cancer and that on a man. Only in one race of Barbars and Arabians near the river Niger did he find an affection of the skin which resembled very much epithelioma of the lip. Livingston and Lantre did not meet cancer in any of the African races. Lantre who spent many years among the Bassuti, a nation north of Cape Colony, did not see one case of cancer of the face, which among the whites of the Cape Colony is not at all rare. Epithelioma of the lip is most frequent in Central Europe which is indeed the most thoroughly known regions.

Dr. M. Grau, of Detroit[1], inquired particularly about the prevalence of tumors among the Sioux, Bannocks and other Indian tribes (with whom General Custer came in conflict at the time of his death) of Dr. Gillycuddy, who for three years past has been acting as assistant surgeon to a regiment of United States cavalry, stationed in that region. The doctor has come in contact with many thousand Indians, and was in medical charge of one of the largest Indian agencies. In an extensive practice among them, in which he had occasion to treat them for almost everything else, he had met with but one tumor of any kind, and that was an atheromatous cyst on the neck of a squaw.

I would like to quote at this place some remarks of Dr. Crisp, of London, made on occasion of a discussion on cancer[2].

"The geographical distribution of the disease, Mr. Haviland has shown, in the cancer-chart which he published, corrected from the records of the tables of the Registrar-General, that there are cancer-fields in England where cancer predominates to an inordinate extent, and that these cancer-fields are associated with certain local peculiarities of soil, geological peculiarities. It is well known, no doubt, to many members of the society that, in those districts where the primitive rocks and the earlier formations principally exist, cancer is comparatively seldom met with; whereas, as you descend the river courses, and get into the tertiary formations, and especially into low-lying alluvia lands subject to overflowing, and other conditions

[1] M. Grau, The Germ Theory of the Etiology of Tumors, Detroit Lancet, 1878, p. 803.

[2] British Med. Journal, 1874.

of that kind, you find cancers developed to a much greater extent. That subject is as yet not worked out sufficiently."

"In country places people constantly marry within a circle. One individual who happens to have a cancerous taint may produce five or six cases of cancer, as they seldom go far from the locality. The prevalence of cancer may be more readily accounted for in that way than by any other influence that locality or soil may exert."

8. *For endemic* conditions influencing the etiology of tumors, Goitre if regarded as a neoplasm would be the only instance.

9. *Acquired predisposition* to tumors. By this I would like to define a predisposition acquired through *external influences*, *i. e.* through anything that may excite an inflammation or a long continued irritation and consequent disturbance in the tissues, *e. g.* injuries, long standing, pressure or irritation, colds, etc. Injuries are properly regarded as ~~existing~~ causes of tumors, but this may only be so in a certain class of cases, perhaps in hereditary tumors. From my inquiries I am inclined to believe that the inflammatory process creates conditions in the tissues which directly and more than any other cause predispose to tumor formation and hence I would regard inflammation a predisposing, rather than an exciting cause. Good and exhaustive statistics should be made in this direction.

exciting

Of all the enumerated causative factors I will give a detailed consideration only to the last one, the "*Acquired predisposition*," suggested by myself. The rest of the supposed factors are all, to my mind, not sufficiently established yet; though some of them, *e. g.* "the evolution and involution of tissues" as conditioned by age, are of great importance in the etiology of tumors.

IV. PERSONAL INVESTIGATION AND ARGUMENTS IN FAVOR OF THE INFLAMMATORY THEORY.

The immediate cause of tumors has been repeatedly traced, beyond doubt, directly to inflammatory processes. Hence an inflammatory theory of the etiology of tumors is not a hypothesis.

The dyscrasia, embryonal, spontaneous and nervous theories,

as ingenious as they are, can hardly, at present, be regarded as theories, but must be called hypotheses; for so far not a single tumor can be proven to have really developed from the causes promulgated. I gave those hypotheses due consideration, but I did not attempt to criticise them for want of time and space; and, again, there is *nothing to be disproven, where nothing is proved.*

I will now enter into some details of the inflammatory view, the one I have adopted.

It is properly held by some that no line of distinction can be drawn between true tumors and chronic inflammatory products. I shall bring forward some facts now generally acknowledged, and also some investigations of my own, which will yet considerably strengthen this view.

Practically we do not know what inflammation really is; we know only some of its causes, symptoms, and some of the terminations. But the inflammatory process itself and some of its terminations have been pretty well studied and are well known through the labors of Virchow, Cohnheim, Stricker, Ziegler, Ranvier and Samuel abroad, and W. F. Norris, Woodward and E. O. Shakespeare in this country. From these observations we also learn that many and sometimes all the signs of inflammation may be wanting in that process, and really, the symptoms are altogether absent in many of the so-called chronic inflammations.

Many of the products of inflammation are not only difficult to distinguish from tumors, but are really recognized as true tumors. The criterion of true tumors is regarded to be their tendency for permanency in contra-distinction to inflammatory products which tend to disappear; but it can be shown that, while true tumors occasionally do disappear, inflammatory products, very frequently, never disappear.

There are many cases of sudden and gradual disappearance of tumors on record. I shall mention only a few.

Dr. Th. Dwight[1] reports a case of an unmistakable tumor of

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[1] Dr. Th. Dwight, The Disappearance of Tumor, Boston Med. and Surg. Journal, 1880, p. 562.

the rectum, which had disappeared spontaneously. In the discussion of the paper the argument was brought forward that, of all tumors, only lymphoma is known to disappear and, as this tumor was single, it probably was not lymphoma, the latter tumor always occurring multiple; the probability being more in favor of its having been medullary sarcoma (commonly mistaken for encephaloid in former time).

Prof. Louis A. Duhring[1] has met in his practice a peculiar tumor, which he has called *inflammatory fungoid neoplasm.* This appeared suddenly as round or oval, circumscribed, nodular or fungoid growth of a dark-red color and of the size of a pea to that of an egg. Having attained a definite size, as a rule, these growths would soften, diminish in volume and undergo sooner or later spontaneous involution without pigmentation and without scar. Although resembling sarcoma, as Dr. Heitzmann of New York pointed out, Dr. Duhring considers that this disease is unquestionably an inflammatory new formation, allied to sarcoma, but differing from it as described by authorities. The great peculiarity of these growths was their rapid rise and fall, rising in a night and disappearing within a week.

H. Fisher[2] records a case of a man from whom a large tumor of the neck had been extirpated; two days after the operation a swelling of a gland, as large as a fist disappeared during a night; at the same time high fever set in and the patient died. Three days later at the post mortem no cause of death could be found. In the axilla was found a small swollen gland. Fisher believed that a very acute fatty degeneration and reabsorption of the tumor elements took place. In a second case a tumor of a lymphatic gland as large as a fist diminished to the size of a small apple during the progress of an acute meningitis and tubercular pericarditis. In a third case during iliotyphus in a girl sixteen years old, a lymphatic tumor of the neck, 5 c. m. long and 3 c. m. wide, diminished to the size of a bean. In a fourth case a goitre disappeared during the

[1] Duhring. See Supplement to a case of Inflammatory Fungoid Neoplasm, by Louis A. Duhring, Phila'a, 1880, pp. 12-16-18,

[2] Deutsche Zeitsch, f. Chirurgie, xii, Heft 1 und 2, 1879.

progress of scarlatina. The author adds a few cases of tumors in which, after trifling interference, noticeable diminution of size occurred.

Berns, of Amsterdam, also records similar instances of the disappearance of tumors.

Lücke[1] also observed tumors diminish and even permanently atrophy under the influence of exhausting diseases.

Virchow[2], says that warts, condylomata and even fibroma have frequently been observed to heal and to disappear, undergoing a slow atrophy and resorption.

Simon[3] records the case of a recurrent fibroid which disappeared completely when treated by cold (?)

Prof. Wm. Goodell[4] says, that fibroid tumors when affecting the womb at a period near the meno-pause, frequently undergo retrograde change. "The climacteric once reached, these growths generally grow smaller and may even disappear."

Even Rindfleisch, in his text-book, records that pediculated tumors have fallen of their own accord, and that entire cancerous nodes have been observed to cast off spontaneously.

Drs. Ripley[5] and Robinson, of New York, each recorded a case of complete disappearance of epithelioma. Dr. Robinson's case was one of epithelioma of larynx which had perfectly healed. Dr. Ripley's case is particularly interesting, as it formed the subject for discussion in the Pathological Society of New York. The case was epithelioma of lip of several years duration, and was not removed on account of the bad health of the patient. Subsequently the new growth spread by extension to both submaxillary glands. While the secondary deposits below the chin continued to grow producing tissue destruction, the original growth on the lip healed and was fully

[1] Lücke, l. c. p. 16.

[2] Virchow, Geschwülste (l. c. p. 350.)

[3] Simon, Discussion on Cancer, Brit. Med. Jour. 1874.

[4] Goodell, Clinical Observations on the Radical Treatment of Fibroid Tumors of the Womb. Transactions Med. Soc'y, State of Penna., 1880.

[5] Ripley, Epithelioma of Lip Spontaneous Healing of the Original Lesion, N. Y. Medical Record, July 16th, 1881. This is only one of the several cases which I have seen recorded since the reading of this paper.

replaced by yellow, [illegible] substance. In the discussion the following points of interest were brought forward by Dr. Satterthwaite and others: Cancer [illegible] heal spontaneously, or a case is [illegible] through an acute inflammatory process [illegible] the healing being a process of cicatrization. The connective tissue proliferation, [illegible] the [illegible] elements of the cancer, to death," and forms [illegible].

I would like to remark here that the healing process of an ordinary granulating [illegible] is precisely the same as in cancer, wherever healing of the latter occurs. Here, like there, healing is accomplished by the new formation of connective tissue, i. e., cicatrization. Poultices, pressure, etc., act beneficially in the healing of ulcers only because they promote the transformation of granulations into scar-tissue and induce a fatty degeneration of superfluous cell masses; they assist the connective tissue in "crowding to death" the exuberant granulations, from which to sarcoma there is only one step. Lücke[1] says, that sarcomata in very young individuals, occasionally grow as rapid as acute abscesses and are frequently mistaken for the latter.

I mention this in order to point out the close analogy that exists in the termination of tumors and that of inflammatory products.

We have seen that tumors occasionally heal and disappear. On the other hand, it is well known that many inflammatory products, particularly chronic ones, never do disappear and that the symptoms and cause of them are frequently less obvious than in the case of tumors. The connective tissue which, in proliferating, constitutes the main bulk of elephantiasis and of the cirrhosis of organs and a good many other pathological tissues outside of tumors, never disappears.

Virchow properly considers elephantiasis arabum and soft fibroma morphologically and etiologically identical and, in the same sense he does not admit any difference between the con-

[1] Lücke, Die allg. chir. Diagnostik d. Geschwülste, Volkmann's Klin. Vorträge, 97, 1875.

nective tissue of an advanced cirrhosis of organs and that of a diffused fibroma. In fact, we are only in the habit of calling a proliferation of connective tissue in the mamma an intercanalicular fibroma, because the connective tissue affects an external part, while a similar affection of the liver or kidney we term an inflammatory one—a cirrhosis. Why should we make such a distinction?

I believe that inflammation is the most prominent cause of tumors. I am also ready to assert that inflammation is not only an exciting, but mainly a predisposing cause of tumors.

Any inflammatory process, due either to external or internal injury or irritation, etc., may produce a new formation of tissue—a tumor. This may depend particularly upon an imperfect process of healing, as I shall show later.

We even do not need here to take into consideration gummata, tubercle, lupus, etc., the well established products of inflammation, which so frequently occur as well defined tumors. I think we can come to a satisfactory conclusion on the inflammatory origin of the true neoplasm even without them.

My own experience is limited, but in the cases of tumors, in which I had the opportunity to get the history myself, or where I insisted upon an exhausted anamnesis in cases of others, it was possible in nearly one-half of the cases to trace out a local inflammatory process preceding the tumors at some time or other. Sometimes it dated years back. Careful inquiries nearly always revealed some cause, viz., an injury, long standing irritation, mechanical or toxic or an impaired or excessive use of the part, pressure, or a long standing catarrh, or something of that nature.

Tissues which are most liable to be the seat of inflammation are also the most *common seat* of tumors. Again, those tissues which do not participate in active inflammatory processes (ganglionic and striated muscular tissue) seldom or never give rise to tumors.

The extensive and careful statistics of Dr. d'Espine of Geneva show that the os uteri and the stomach are the most frequent seats of primary cancer, and they are also distinguished for their remarkable liability to catarrhs. Virchow has repeatedly

pointed out in a catarrhally inflamed gastric mucous membrane the gradual transition to carcinoma.

Dr. J. H. Musser directed my attention to the fact that primary cancer of the gall-bladder is nearly always preceded by gall-stones. He demonstrated a beautiful specimen of recently developed cancer of the gall-bladder to the Pathological Society of Philadelphia, in which the clinical history revealed gall-stone for years. In looking up the literature, Dr. Musser found numerous cases of primary cancer of gall-bladder, and every one was preceded and accompanied by gall-stones. Unquestionably in all these cases the stones excited a catarrhal inflammation and this produced the cancer. A gradual transition from catarrhal inflammation of the mucous surface of the gall-bladder and duct to cancerous formation was distinctly demonstrated in the microscopic preparations from Dr. Musser's case.

I have on several occasions contributed[1] to prove, that most of the so-called indolent ulcers are epitheliomata; nearly all those everlasting ulcers are surface cancers. But at one time they were little sores and were produced by an injury. There is a number of these indolent ulcers in Philadelphia hospitals, they are all due to inflammation, which is directly traceable. I examined many of them microscopically, and nearly every one proved to be an epithelioma.

Dr. S. W. Gross[2] is of the opinion that cancer of breast may result from ordinary eczema or psoriasis of the nipple, just as epithelioma of the tongue may follow ichthyosis or hyperplasia of the epithelium of that organ. Dr. Gross finds from his own statistics, that non-carcinomatous tumors, too, have been traced to a trauma in one example out of every eight and a half cases.

Dr. A. P. Gerster[3], presented recently to the Pathological Society in New York three specimens, which illustrated beautifully the traumatic origin of cancer. The first case was a

[1] See Transactions of Path. Society of Philadelphia.

[2] Gross, Tumors of Mammary Gland, 1880.

[3] Gerster, Specimen illustrating the Traumatic Origin of Cancer. *N. Y. Medical Record*, July 16th, 1881.

cancer of the sole of foot, which had killed the patient by metastasis of the growth to the brain and nearly all other inner organs. The doctor had observed the case for years, and had traced with absolute positiveness the primary tumor of the foot to a simple erosion of the skin from stepping on a nail. The second case was cancer of the outer malleolus, also directly formed at the seat of injury. The third case was a cancer of the lower extremity, developed directly in a scar, the result of a burn dating thirty years back. The tumor did, however, not develop until a year prior to the amputation, when he had struck himself accidently upon the same spot.

I have seen myself, several similar cases of tumors positively of traumatic origin in the University hospital clinic and elsewhere. As some of them are and others will be recorded in the proceedings of our Pathological Society, I will refrain from mentioning them here individually.

Winkel[1], who investigated exhaustively the etiology of myomata of the uterus, came to the conclusion that these tumors are caused either by direct exitents, viz.: coition, injury, abortion, rough removal of placenta, cellulitis; or indirectly: through repeated lifting, shock, sudden hyperæmia, etc. "These," he says, "inevitably first produce disturbance of circulation, stasis and wandering out of white blood corpuscles, etc." What do we need more; is it here not plain that the inflammatory process was the causative factor of the new growth? The author, however, unnecessarily adds: "this extravasats or transudats gives the impulse for the new-formation like an ovulum, etc."

Epithelioma of lips, one of the most common tumors, gives a clinical proof of the inflammatory theory; here the irritation by the tobacco-juice, as well as the pressure of the pipe, must be the cause, as the new growth occurs pre-eminently in men who are inveterate smokers.[2] I examined the teeth in three cases of epithelioma of the tongue; in every case they were bad, many being broken, and had been in that condition for

[1] Winkel, Volkmann's Samml. Klin. Vorträge, No. 98.

[2] I once saw an epithelioma of the lip in an Irish woman; upon inquiries I learned, however, that she had indulged in smoking a short pipe for many years.

years, probably the irritation and injury to the tongue were the cause of the new-formation. Similar observations have been made by others.

Epithelioma of penis has repeatedly been traced to a congenital or acquired phimosis, a condition which naturally gives rise to constant irritation and usually calling forth an inflammation.

The workmen in coal-tar and paraffine manufactories suffer very frequently from acute and chronic inflammations of the skin. Volkman[1] has already described several cases in which true epithelial cancer was developed from those chronic inflammations, and Tellman[2] now adds another of the same nature, ending fatally after numerous operations. This form of cancer has a parallel in the chimney sweeper's cancer.

Most of the myelinic neuromata occur only in amputated stumps, developing at the cut ends of nerves, and hence are direct inflammatory products. (Perls.)

Frequently warts, nævi and keloids,[3] through interference which sets up an inflammation, increase and multiply, and even are converted with malignant tumors.

Lücke and Virchow found that whenever an autopsy revealed cancer or any tumor of stomach or œsophagus, the clinical history nearly always revealed "*drunkard.*" We have seen before that from long-continued catarrh to carcinoma there is only one step.

Lipomata very frequently occur in portions of the body which were subject to excessive pressure or irritation. Probably, however, we must first have the development of connective tissue, a fibroma, before we have a lipoma.

Extremely frequent is the occurrence of sarcoma in young persons in consequence of direct injury, or developing in any imperfectly healed scars. Hundreds of cases of chondroma

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[1] Volkman, Sammlung Klin. Vorträge.

[2] Tellman, Deutsche Zeitschr. für Chir., Vol. XII.

[3] Concerning keloids I would like to remark that, as is well known, most of them consist morphologically of cicatrical tissue. Surgeons who remove them find that they always return. They do not return, but the *scar tissue* returns—as in loss of substance true skin is never reproduced, but only a scar.

and osteoma, too, have been traced by a distinct and clear history and evidence directly to blows, fractures, cuts and other injuries.

Any one can convince himself of the above-mentioned facts by just looking carefully over the literature, and by taking careful histories of his own cases. Hundreds of tumor cases of positively traumatic origin are also recorded in the classical works on tumors of Virchow, Weber, Müller and Broca. All the present younger working pathologists in Europe are in favor of an inflammatory origin of tumors, though none of them expresses himself definitely, still they return gradually to the view which the fathers of Pathology held originally.

Inflammation is the only factor which has been traced to be the positive cause of tumors in a number of cases. This is proven by high authority and statistics. But as these authenticated cases of inflammatory origin are in moderate number, and as those with no cause, by reason of careless note taking, are in enormous majority, the inference is drawn that inflammation has little or no significance in the pathogenesis of tumors.

I beg leave to argue as follows: In a certain number of cases it is positively known that inflammation preceded and was the cause of the new growth. In regard to the remaining cases of tumors we know nothing, no positive cause could be traced. Hence I think it logical, for the present, to consider inflammation as the cause of tumors in general[1]. All other alleged causes are only speculations; and nothing reasonable can be brought forward against the inflammatory theory. Speculations are valueless, I think, in the presence of positive facts, even if these be few in number. In science any amount of negative results are always disregarded in the presence of even a few positive facts. *Until contrary proof be given we are at present, by a mass of evidence, forced to the conclusion, that tumors represent merely one of the terminations of inflammation.*

The question now arises in what way does inflammation

[1] I would exclude here only the purely congenital new-formation, *e. g.* simple Angioma, and Lymphangioma, Rhabdo-myoma, the dermoid cysts and a few of the nævi. These are simple congenital anomalies of the organism.

produce a tumor, and why and when does a tumor develop after an injury? Why is not every injury followed by a tumor if inflammation is the cause? Prof. Maas[1] ingenious answer was, that it depends upon the presence or absence of Cohnheim's supernumerary embryonic cells at the seat of the injury. If those misplaced or aberrant cells happen to be present in a part, a trauma will induce inflammation followed by a tumor; if no extra cells are present, a simple inflammation will follow and nothing more. But this is only a hypothesis, it cannot be demonstrated. Embryonal (fœtal) cells could not continue to exist unchanged in the adult individual; nor do they need to be pre-existing in order to form a tumor. They can be and are always created by any inflammatory process.

I will try to answer the above question by facts, which microscopic examination reveals and which will show that the study of histogenesis must go hand in hand with that of the etiology and possibly might disclose the mysteries of the cause of tumor.

It is true that not always direct observation of active pathological processes can be made. In the case of tumors only inferences of previous cell activity can be drawn from the microscopic picture; but the pathological process can frequently be traced out under the microscope, from the various transitional stages of the elements of the new forming or formed tissue.

It is in accordance with the modern views to say that every tumor has its strict physiological prototype. Even for the cancer, only the peculiar atypical arrangement of the cells remained a criterion, while the cells themselves are supposed to be strictly identical with those found normally.

It appears to me, and the more I study the histology of tumors the more I become convinced, that any variety of cells composing a tumor are not identical with those found normally but resemble those met with in chronic inflammatory products.

In tumors, the shape and the peculiar variations in size of the cells and nuclei, the character of the intracellular network,

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[1] Maas, Berliner Klin. Wochenschrift, No. 47, 1880.

and of the amœboid motion of certain cells, the intercellular substance, the occasional arrangement into nodes, the relation to reticulum and blood vessels, and the peculiarity of the latter are all precisely like what is found in chronic inflammatory products and not like in normal tissues.

There is a great difference between the tissue elements of fibroma and those of normal connective tissue, for example.

I shall give briefly the details of my investigation of the structure of fibroma which, when completed, will be published and illustrated elsewhere.

Concerning the structure of normal connective tissue, the following seems to be generally established and in good preparations quite demonstrable:

The ultimate connective tissue fibrils (the fibrillar variety) are in varying number united together to form bundles; these again occasionally unite to form larger bundles; these bundles arrange themselves at different localities in various manner, *i. e.*, parallel as in tendons, or as a lattice work in membranes, or decussate at different angles and in all possible directions in all other localities, leaving between small spaces. These spaces being dependent for their shape and size upon the arrangement of the bundles. They communicate with one another and thus form a system of channels throughout the whole connective tissue system of the body. These channels contain a small amount of fluid containing *Mucin*, and they are the receptaculi of the sometimes enormous quantities of serum in œdema. These same spaces or channels may also get filled with air producing emphysema in skin and other parts of the body[1].

v. Recklinghausen has shown that the spaces in the connective tissue communicate with the lymphatics, and he calls the spaces, juice channels; they act as "vasa serosa," (Orth), conducting the serum from blood vessels to the lymphatics, and "feeding" (Tyson) the tissues.

[1] The subcutaneous tissue of the whole body can be filled with air so as to produce enormous emphysematous disfiguration, by forcing air through blow-tubes at a few points or possibly even from only one point of the body below the skin. I have seen children purposely prepared in this way for beggars purpose.

By the nitrate of silver method, of v. Recklinghausen, which is now the common property of all the laboratories of the world, it can be easily demonstrated that each of the connective tissue bundles spoken of is surrounded by a distinct membrane composed of large flat cells. These flat, so-called endothelial cells are very thin, nucleated and are closely united at their periphery with one another, so as to form continuous membranes or sheaths, which envelope each or several fibrillar bundles, and thus at the same time form a lining for the spaces between them. Without nitrate of silver the endothelial cells cannot be seen; all that is seen are the nuclei of the cells: round or oval in shape if viewed from above, or spindle shape if the whole cell is seen in profile. I will not enter into further details here; this suffices to make myself now intelligible concerning some points in the histology of connective tissue tumors, particularly fibroma.

I investigated by the nitrate of silver method three specimens of fibroma: 1st, a small, hard fibroma from the finger of a girl, æt. 20, developed from the tendon; 2d, one of the size of two fists from the broad ligament of a woman, æt. 35, and 3d, an intra-uterine fibroma of the size of one fist from a woman, æt. 40.

I might say at the outset that in the preparation of the first and third specimens I failed altogether to discover any perfect endothelial sheaths surrounding the bundles of fibres, which were so beautifully seen in a preparation of tendon, made for comparison simultaneous with the fibroma specimens. In specimen 2d only a few perfect endothelial sheaths were visible. The microscopic picture of one of the silver preparations (from specimen No. 1) was this: The fibrils were on the average much thicker than in normal connective tissue; some running straight, others rather wavy and not quite parallel with one another, frequently decussating. Only few perfect fasciculi or bundles of fibres were seen, but most of them had not a trace of endothelial ensheathment. Some had a partial endothelial sheath in some places, and here the bundles appeared constricted. In several places were seen irregular protoplasmic masses apparently in connection with the fasciculi and proved

to be partially detached endothelial cells. Between the bundles were seen several groups of young indifferent cells, resembling white blood corpuscles. Other cells were double the size of the latter, some spindle shaped and with prominent nuclei. The latter were seen occasionally in a state of division or were already divided. They resembled remarkably the germinating endothelial cells from serous surfaces, as described by E. Klein of London, represented by him in his Atlas of Histology, plate VI.

I interpret the microscopic picture as a whole thus: The endothelial cells composing the sheaths of bundles of connective tissue have become isolated and hence the sheaths are destroyed. The boundaries being removed, the liberated connective tissue elements grow with great vigor. The growth is perhaps promoted, yet more by the presence of the serum of the juice channels, with which the cellular and fibrillar elements now come in direct contact, the sheaths being destroyed. The cells and fibres here, like in elephantiasis, "feed" (as Prof. Tyson would say) upon that serum in which they are soaking. The endothelium is proliferating (germinating, *Klein*) and probably gives rise to those groups of indifferent cells, which evidently form the main source of the new growth. Foerster[1] has pointed out that in the development of fibroma the fibres arrange themselves more or less concentrically around and develop from these islands of cells, thus giving rise to the lobulated appearance of this new growth. It is also very probable that emigrated white blood corpuscles assist in forming those collections of cells.

What interests us at present, however, is the absence of the endothelial sheaths in the connective tissue bundle in the fibroma, and that this feature fibroma has in common with all connective tissue formations which owe their origin to inflammation as will be shown directly.

I can affirm the absence of endothelial sheaths in the new formed fibrillar connective tissue as met with in cirrhosis of organs which invariably accompanies the proliferation of the

[1] Foerster, Atlas der mikroskopischen and pathologischen Anatomie, Leipzig, 1855.

alveolar connective tissue in such situations. It would be very desirable that other histologists would undertake research in this direction.

Cornil and Ranvier[1] describe the disappearance of the endothelial ensheathments in connective tissue which is the seat of inflammation. They describe the appearances as follows: "The fasciculi are smaller; less distinctly fibrillar; they do not appear to be enveloped by a special layer which limits them and which causes them to swell irregularly when acted upon by actetic acid." C. and R. consider that the "large flat cells" are replaced by embryonic tissue.

The inflammatory process is, to my knowledge, the only factor which can disconnect or isolate endothelial or epithelial cells united together to form a certain lining or covering. Let us take, as an instance, the lung. The flat cells which form the lining of the air-vesicles, are so closely united or grown together in the normal adult individual, that no means at our command at present can isolate them. But in catarrhal pneumonia the inflammatory process demolishes that lining instantly, the cells which compose it "return to their embryonic state" (Stricker), they become completely isolated.

The abnormal increase in bulk of tissue in both the fibroma and the inflammatory connective tissue products, appear to me to be due to the same cause:

1. The removal of the boundaries which keep the fibres in tact, viz.: the destruction of the endothelial ensheathments.

2. The proliferation of the endothelial cells of these destroyed sheaths and of the connective tissue elements themselves, and probably with the aid of white blood corpuscles.

If the endothelial sheaths of the connective tissue bundles and other normal boundaries are re-established in the inflamed tissue, then it will return to its normal state, or in case of loss of substance will heal by permanent scare tissue. The healing process was perfect.

On the other hand, the same tissue will give rise to a fibroma

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[1] Cornil and Ranvier, a Manual of Pathological Histology, translated by Shakespeare and Simes, Philadelphia, 1880.

if this healing process was imperfect, *i. e.*, the endothelial ensheathments are not reestablished, the connective tissue elements remaining freed from any restriction proliferate on their own accord, grow above the physiological limit, and thus inflammation terminates in a tumor.

Hence, from histogenetic grounds, I would suggest: that *Fibromata should be classed as a product or rather as one of the terminations of inflammation.*

This is also in accord with clinical experience.

Now, is an inflammatory origin less evident in other tumors? Can there be shown any positive microscopic difference, for instance between a mass of inflammatory granulation tissue and a sarcoma? It cannot. To my knowledge, distinguished histologists have repeatedly had sad experience in this.

If the discoveries of Classen and Woodward should prove correct, we would, to my mind, have another additional proof that cancer is only one of the terminations of inflammations. I will quote the following:

Woodward[1] says: "My own studies of thin sections lead me to the conclusion that the migration of white blood corpuscles played a great role in the development of cancerous growths, and that at least in certain cases the cancer cylinders were formed by the transformation of these corpuscles, which first accumulated in the lymphatic capillaries and the passages leading to them."

Classen[2] is even still more positive, saying that he has proven "that the cells of cancer cylinders and all the elements of cancerous growths are no other than migrated white blood corpuscles escaped from the blood-vessels."

Though in my own research I did not succeed as yet to confirm the observations of Woodward and Classen, they are possibly correct, and I utilize them as coming from such high authority. Besides, they correspond so remarkably to what I believe to have established for fibroma.

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[1] Woodward, on The Structure of Cancerous Tumors. Toner Lectures, Washington, 1873.

[2] Classen, Ueber Cancroid der Cornea, etc. *Virchow's Archiv.*, Vol. 50, 1870.

My view of the histogenesis of fibroma holds good also for primary glandular carcinoma.

The glandelemma or basement membrane in glands (wherever such exists), upon which the epithelial cells rest, may be destroyed in precisely the same manner as the endothelial sheaths of the fibrillar bundles. This is demonstrable in carcinoma beginning to develop in a gland, or in the transformation of an adenoma into cancer. Here as in fibroma only an inflammatory process can accomplish this destruction of the normal boundaries. These boundaries, if not reestablished after an injury by perfect healing, the epithelial cells once loose and free, there is nothing remaining to prevent them from travelling into surrounding connective tissue spaces and to thus form a cancer.

It is not the want of resistance of the surrounding tissue (as is generally held), but simply the getting loose of the normal cells from their place of attachment, which constitutes the formation of a malignant tumor.

It is the mobility of the cells, I think, that conditions the malignancy of a tumor. Any tumor, even the most benign lipoma, would be eminently malignant, if the cells composing it could get loose and travel through the widely open paths of the system of juice channels.

It would appear that I have deviated from the scope of my subject; but I think all these points considered have a direct bearing upon the etiology of tumors. Of course, I consider this communication nothing more than an attempt at the solution of the etiology of tumors. It is a complete compilation of all known facts and theories with a few additional original contributions. I hope it may suggest some thoughts and encourage others to undertake research on this subject, which, I believe, will establish the fact, that *all tumors are products of the inflammatory process, and that they should be considered as one of the terminations of inflammation.*